SUBJECT:	IMPLEMENTATION DATE:
Medicated Feed Manufacturing Compliance Program	**UPON RECEIPT**
	COMPLETION DATE: **Continuing**

DATA REPORTING	
INDUSTRY CODE	PRODUCT/ASSIGNMENT CODES (PAC)
69 (Medicated Animal Feeds)	**71004** (Medicated Feed Manufacturing CGMP) **71S004** (State Contract - Medicated Feed Manufacturing)

FIELD REPORTING REQUIREMENTS:

When an Office of Human and Animal Food Operations (OHAFO) Division becomes aware of any significant adverse information that affects the Agency's licensing decisions on a firm, the OHAFO Division should immediately notify the Center for Veterinary Medicine (CVM) Division of Compliance, HFV-230, by email at CVMCompliance@fda.hhs.gov; HFV-230, in turn, will convey the information to other interested CVM units.

Send copies of the Investigational Memo for those Out-of-Business (OOB) or Not Official Establishment Inventory (NOEI) firms to CVM's Division of Animal Feeds (HFV-220) by email to MedicatedFeedsTeamMail@fda.hhs.gov or hardcopy via USPS (FDA/CVM, Division of Animal Feeds, HFV-220, 12225 Wilkins Avenue, Rockville, MD 20852).

Forward a copy of Attachment A – Sample Form Letter Issued by OHAFO Division to Firm to Request Voluntary Withdrawal of an Approved Medicated Feed Mill License to CVM's Division of Animal Feeds (HFV-220).

Forward copies of all Warning Letters to CVM, HFV-236, Animal Food Program Team. (see Part VI.3. for contact information)

When there is a change to the firm's name, address or responsible person, the firm should:

- submit a supplement to their medicated feed mill license
- update their drug registration
- update their food facility registration

When there is a change in ownership the firm should:

- withdraw or transfer their medicated feed mill license to the new owner
- update their drug establishment registration
- update their food facility registration

Direct the firm to contact CVM's Division of Animal Feeds, HFV-220 via email at MedicatedFeedsTeamMail@fda.hhs.gov for further information.

For Current Good Manufacturing Practice (CGMP) medicated feed inspections charge time to PAC 71004, or 71S004 for state contract inspection. If the inspection covers both the manufacturing of Type A Medicated Articles (CP 7371.005/PAC 71005) and manufacturing of medicated feeds (CP 7371.004/PAC 71004), be sure to include both PACs on the coversheet. For bovine spongiform encephalopathy (BSE) (CP 7371.009) use the appropriate codes listed within that program.

Change History

Program remains current; program name modified. Changes made to provide better clarity and organization of the information in the Compliance Program, and to reflect Veterinary Feed Directive regulation changes, program contacts, data codes, and references.

Table of Contents

PART I - BACKGROUND

1. Overview

This Compliance Program (CP) provides direction to field staff for conducting activities to evaluate medicated feed firm's compliance with the requirements for animal food and medicated feed under the Federal Food, Drug, and Cosmetic Act (FD&C Act) and related regulations in the Code of Federal Regulations (CFR). This CP primarily focuses on the requirements for medicated feed firms that are required to be licensed as a medicated feed mill. The CP also discusses other requirements that may be relevant to both licensed and non-licensed medicated feed firms.

The term “animal feed” is defined in Chapter II, section 201(w) of the FD&C Act as an article intended for use for food for animals other than man and which is intended for use as a substantial source of nutrients in the diet of the animal, and is not limited to a mixture intended to be the sole ration of the animal. The FD&C Act and related regulations in Title 21 Code of Federal Regulations (21 CFR) § 558.4 provide for approved uses of new animal drugs and combinations of new animal drugs in animal feed. This document uses the term "medicated feed" to refer to animal feed containing these drugs and the term “animal food” when discussing information that is relevant to both medicated feed and non-medicated animal food.

Medicated feed is an animal food that contains a drug, in the form of a Type A medicated article, and animal food ingredients. Type A medicated articles can be mixed with animal food ingredients to produce a:

- Type B medicated feed, which contains a concentrated amount of the Type A medicated article along with other nutrients, but is not to be fed directly to animals.
- Type C medicated feed, which contains an appropriate amount of the Type A medicated article to be fed directly to animals. See Definitions.

Any new animal drug approved for use in animal feed is placed in one of two categories, Category I or II. See Definitions. Medicated feed firms that handle Category II Type A medicated articles are required to register as drug establishments and obtain a medicated feed mill license.

2. Veterinary Feed Directive

In 1996, Congress enacted the Animal Drug Availability Act (ADAA) (Pub. L. 104–250) to facilitate the approval and marketing of new animal drugs and medicated feeds. In passing the ADAA, Congress created a new regulatory category for certain animal drugs used in or on animal feed called veterinary feed directive drugs (or VFD drugs). VFD drugs are new animal drugs intended for use in or on animal food which are limited to use under the professional supervision of a licensed veterinarian. The regulations for the authorization, distribution, and use of VFD feeds are in 21 CFR § 558.6. Relevant definitions for these requirements are found in 21 CFR § 558.3.

In 2013, to promote the judicious use of antimicrobials FDA recommended that certain medically important antimicrobials in food-producing animals administered in or on animal food change from an over-the-counter marketing status, to a veterinary feed directive marketing status by January 1, 2017.[1] Drug sponsors implemented this recommendation, which significantly increased the number of new animal drugs with VFD marketing status. In anticipation of this increase and in recognition of the need to improve the VFD program's efficiency, we finalized changes to the VFD rule on June 3, 2015 (80 FR 31708).

Like Over-The-Counter (OTC) drugs approved for use in animal feed, VFD drugs are also categorized as Category I or Category II drugs. VFD feeds are subject to the same licensure and medicated feed CGMP requirements as other medicated feeds. In addition, there are requirements for the authorization, distribution, and use of VFD feeds in 21 CFR § 558.6.

3. Definitions

Animal Feed: The term "animal feed" as it relates to the definition of new animal drugs is defined in Chapter II, section 201(w) of the FD&C Act as an article intended for use for food for animals other than man and which is intended for use as a substantial source of nutrients in the diet of the animal, and is not limited to a mixture intended to be the sole ration of the animal. (21 CFR § 510.3(h))

Animal Food: Animal food means food for animals other than man and includes pet food, animal feed, and raw materials and ingredients. (21 CFR § 507.3)

Blue Bird Labeling: Representative Type B and/or Type C medicated feed labeling approved in the Type A medicated article New Animal Drug Application (NADA). This template is used by manufacturers as a model to generate actual feed labels.

Carryover: Cross-contamination of animal food during manufacturing with a drug used to manufacture a previous batch of medicated feed.

Category I: These drugs require no withdrawal period at the lowest use level in each major species for which they are approved or are approved for use only in minor species. (21 CFR § 558.3(b)(1)(i))

Category II: These drugs require a withdrawal period at the lowest use level for at least one major species for which they are approved, or are regulated on a "no-residue" basis or with a zero tolerance because of a carcinogenic concern regardless of whether a withdrawal period is required

[1] The recommendation to change marketing status for certain medically important antimicrobials was published in Guidance for Industry #209, The Judicious use of Medically Important Antimicrobial Drugs in Food-Producing Animals. The timeline for implementing this recommendation was published in Guidance for Industry #213 New Animal Drugs and Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209 (GFI# 213).

in any species. (21 CFR § 558.3(b)(1)(ii))

Commercial Feed Mill: A feed mill that combines and/or mixes feed that is distributed or intended to be distributed for use as animal food or for mixing in animal food.

Custom Formula Mixer: A feed mill that mixes animal food or animal food ingredients according to the specific instructions of the final customer, which are distributed only to that customer and are not redistributed.

Distributor (as it pertains to Veterinary Feed Directives): Any person who distributes a medicated feed containing a VFD drug to another person where the other person may be another distributor or the client-recipient of a VFD. (21 CFR § 558.3(b)(9))

Flushing: The process of running animal food, usually an abrasive-type material such as corn, soybean meal, peanut hulls, etc., through the manufacturing equipment and associated handling equipment (e.g., conveyors) after the production of a batch of medicated feed, for the purpose of cleaning out any drug residue.

Free-choice Medicated Feed: Free-choice medicated feed is medicated feed that is placed in feeding or grazing areas and is not intended to be consumed fully at a single feeding or to constitute the entire diet of the animal. Free-choice feeds include, but are not limited to, medicated blocks (agglomerated feed compressed or rendered into a solid mass and cohesive enough to hold its form), mineral mixes, and liquid feed tank supplements ("lick tank" supplements) containing one or more new animal drugs. The manufacture of medicated free-choice feeds is subject to the current good manufacturing practice regulations in 21 CFR § 225. (21 CFR § 510.455)

Liquid Feed: 21 CFR § 558.5 states that any new animal drug intended for use in liquid feed must be approved for such use under section 512 of the FD&C Act or index listed under section 572 of the Act. Such approvals under section 512 of the Act must be: (1) An original NADA, (2) A supplemental NADA, or (3) An abbreviated NADA.

Mixer-Feeder: This is an operation that mixes animal food, which is fed to its own animals or animals under its control.

New Animal Drug: A new animal drug is defined, in part, as any drug intended for use in animals other than man, including any drug intended for use in animal feed but not including the animal feed, the composition of which is such that the drug is not generally recognized as safe and effective for the use under the conditions prescribed, recommended, or suggest in the labeling of the drug (21 U.S.C. § 321(v); 21 CFR § 510.3(g)).

Type A Medicated Article: A "Type A medicated article" is intended solely for use in the manufacture of another Type A medicated article or a Type B or Type C medicated feed. It consists of a new animal drug(s), with or without carrier (e.g., calcium carbonate, rice hull, corn, gluten) with or without inactive ingredients. The manufacture of a Type A medicated article requires an application approved under 21 CFR § 514.105 or an index listing granted under 21 CFR § 516.151. (21 CFR §558.3(b)(2))

Type B Medicated Feed: A "Type B medicated feed" is intended solely for the manufacture of other medicated feeds (Type B or Type C). It contains a substantial quantity of nutrients including vitamins and/or minerals and/or other nutritional ingredients in an amount not less than 25 percent of the weight. It is manufactured by diluting a Type A medicated article or another Type B medicated feed. The maximum concentration of animal drug(s) in a Type B medicated feed is 200 times the highest continuous use level for Category I drugs and 100 times the highest continuous use level for Category II drugs. The term "highest continuous use level" means the highest dosage at which the drug is approved for continuous use (14 days or more), or, if the drug is not approved for continuous use, it means the highest level used for disease prevention or control. If the drug is approved for multiple species at different use levels, the highest approved level of use would govern under this definition. The manufacture of a Type B medicated feed from a Category II, Type A medicated article requires a Medicated Feed Mill License Application approved under 21 CFR § 515.20.

Type C Medicated Feed: A "Type C medicated feed" is intended as the complete feed for the animal or may be fed "top dressed" (added on top of usual ration) or offered "free-choice" (e.g., supplement) in conjunction with other animal feed. It contains a substantial quantity of nutrients including vitamins, minerals, and/or other nutritional ingredients. It is manufactured by diluting a Type A medicated article or a Type B medicated feed. A Type C medicated feed may be further diluted to produce another Type C medicated feed. The manufacture of a Type C medicated feed from a Category II, Type A medicated article requires a Medicated Feed Mill License Application (Form FDA 3448) approved under 21 CFR § 515.20. (21 CFR § 558.3(b)(5)), A Type B or Type C medicated feed manufactured from a drug component (bulk or "drum-run" (dried crude fermentation product)) requires an application approved under 21 CFR § 514.105 or an index listing granted under 21 CFR § 516.151).

Veterinary Feed Directive (VFD) drug: A VFD drug is a drug intended for use in or on animal feed which is limited by an approved application filed pursuant to section 512(b) of the FD&C Act, a conditionally approved application filed pursuant to section 571 of the FD&C Act, or an index listing under section 572 of the FD&C Act to use under the professional supervision of a licensed veterinarian. Use of animal feed bearing or containing a VFD drug must be authorized by a lawful veterinary feed directive. (21 CFR § 558.3(b)(6))

Veterinary Feed Directive (VFD): A "veterinary feed directive" is a written (nonverbal) statement issued by a licensed veterinarian in the course of the veterinarian's professional practice that orders the use of a VFD drug or combination VFD drug in or on an animal feed. This written statement authorizes the client (the owner of the animal or animals or other caretaker) to obtain and use animal feed with a VFD drug or combination VFD drug to treat the client's animals only in accordance with the conditions for use approved, conditionally approved, or indexed by the FDA. (21 CFR § 558.3(b)(7))

VFD Acknowledgement Letter: An acknowledgment letter is a written (nonverbal) communication provided to a distributor (consignor) from another distributor (consignee). An acknowledgment letter must be provided either in hardcopy or through electronic media and must affirm: (i) That the distributor will not ship such VFD feed to an animal production facility that does not have a VFD, (ii) That the distributor will not ship such VFD feed to another distributor

without receiving a similar written acknowledgment letter, and (iii) That the distributor has complied with the distributor notification requirements of 21 CFR § 558.6(c)(5).

4. Registration and Licensing

A. Food Facility Registration

Domestic and foreign facilities that manufacture, process, pack, or hold food for human or animal consumption are required to register as a food facility with the FDA, unless an exemption applies (see 21 CFR § 1.226 and § 1.227).[2] The failure to register a food facility in accordance with section 415 is a prohibited act under section 301(dd) of the FD&C Act (21 U.S.C. 331(dd)). Facilities are required to renew registrations with FDA biennially.[3]

In most instances medicated feed firms will be required to register because they manufacture, process, pack, or hold animal food. Some medicated feed firms may be exempt if they meet the definition of a farm, because farms are not required to register as a food facility although they may still need to register as a licensed medicated feed mill.

Another exemption to the requirement to register is for "retail food establishments." It is very unlikely that this exemption would apply to a medicated feed firm. In the preamble for the final rule we discussed the definition of retail food establishment related to establishments that sold animal food (68 Federal Register 58960 - 58914). We stated that:

> [T]he definition of "retail food establishment" includes animal food retailers. FDA believes that this is consistent both with including animal feed as "food," as well as with the language of the Bioterrorism Act. The agency has amended the definition of "retail food establishment," however, to clarify that the term "consumers" does not include businesses. As a result, an establishment that sells animal food to pet owners and other individuals as its primary function is exempt as a retail food establishment. An establishment that sells animal feed to businesses, such as farms, as its primary function must register.

For further information see:

> Compliance Policy Guide – Registration of Food Facilities Under the Public Health Security and Bioterrorism Preparedness and Response Act of 2002

[2] Section 305 of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (the Bioterrorism Act) (Pub. L. 107-188) amended the FD&C Act by adding section 415, which established requirements for food facilities to register with FDA.

[3] The FDA Food Safety Modernization Act (FSMA) (Pub. L. 111-353), enacted on January 4, 2011, amended section 415 of the FD&C Act to in part: (1) require the submission of additional registration information and assurances; (2) require registration renewal biennially; and (3) hold imported food at the port of entry until a foreign facility is registered.

Registration of Food Facility website –

https://www.fda.gov/food/guidance-regulation-food-and-dietary-supplements/registration-food-facilities-and-other-submissions

B. Drug Establishment Registration

Manufacturing facilities that hold an approved medicated feed mill license are required, under 21 CFR part 207 (207.13(g)) to electronically register as a drug establishment with the FDA. FDA is required to inspect these firms, utilizing a risk-based inspection priority. Non-licensed facilities are not required to register as a drug establishment. (see Resources for Registering)

A drug that is manufactured, prepared, or processed in a facility that is not properly registered as a drug facility is considered misbranded. (Section 502(o) of the Act).

C. Medicated Feed Mill License

The passage of the Animal Drug Availability Act (ADAA) in October of 1996, amended the FD&C Act to require a single medicated feed mill license to manufacture medicated feed. Regulations governing medicated feed mill licenses are found in 21 CFR part 515.

An approved medicated feed mill license, Form FDA 3448, is required for facilities that manufacture:

- feed using Category II, Type A medicated articles (21 CFR § 558.4(a));
- all free-choice medicated feeds that contain a Category II drug (21 CFR § 510.455(f)(1));
- free-choice medicated feeds that contain a Category I drug and use a proprietary formula or specifications (21 CFR § 510.455(f)(2));
- all liquid medicated feeds that contain a Category II drug (21 CFR § 558.5(g)(1)); and
- liquid medicated feeds that contain a Category I drug and use a proprietary formula and/or specifications (21 CFR § 558.5(g)(2)).

FDA is required to inspect licensed firms according to CGMPs for medicated feeds, 21 CFR part 225, section 225.10 to 225.115. Before a license is approved a pre-approval inspection is required to establish that a medicated feed firm has demonstrated their methods and controls for manufacturing medicated feed will preserve the identity, strength, quality, and purity of the new animal drug and that the manufacturing of the medicated feed meet the CGMP requirements and conditions of the drug approval. FDA will inspect non-licensed medicated feed mills as needed under 21 CFR part 225, section 225.120 to 225.202.

A medicated feed mill license is not required for manufacture of Type B or Type C medicated feeds from a Category I, Type A medicated article with the exception of certain liquid and free-choice medicated feeds (as noted above). When drugs from both categories are in combination, the Category II (licensed mill CGMPs) requirements will apply to the combination drug product

(21 CFR § 558.4(e)). Additionally, a license is not required for manufacturing with Type B or Type C medicated feeds containing either Category I or II drugs.

Contact CVM's Division of Animal Feeds (HFV-220) at MedicatedFeedsTeamMail@fda.hhs.gov when there is a question about whether a firm has or needs to have an approved medicated feed mill license.

PART II - IMPLEMENTATION

1. Objectives

- To conduct inspections of medicated feed firms and determine whether the firms are in compliance with the FD&C Act and the implementing regulations.
- To address concerns of subpotent, superpotent and drug residue carryover in medicated feeds.
- To verify compliance with VFD requirements if relevant.
- To encourage voluntary corrective action by firms when appropriate.
- To initiate advisory or enforcement action against violative firms and medicated feed or animal food.

2. Program Management Instructions

This program uses inspectional observations to determine whether the medicated feed firm inspected is in compliance with the CGMP requirements listed in 21 CFR part 225, the medicated feed mill license regulations in 21 CFR part 515, and the new animal drug regulations in 21 CFR part 558. When conducting inspections at feed manufacturers, feed facilities, and farms, adhere to biosecurity procedures as detailed in Field Bulletin #60 and in the Investigations Operations Manual (IOM) Section 5.2.10. As per Field Bulletin #60, routine on-farm inspections are to be pre-announced.

A. Inspection Priorities

CVM uses risk-based criteria for inspection of medicated feed firms requiring a license. At the beginning of each fiscal year a work plan assignment will issue from the Center identifying which facilities to inspect. The list will include the ranking order of each medicated feed firm within each OHAFO division. As always, the first priority is directed inspections (e.g., for cause). Please schedule inspections in the following priority order:

1. Directed Inspection (e.g., For Cause) (Priority 1)

Conduct directed inspections when there is a public health concern potentially associated with the medicated feed, such as animal illness or death. The potential for a public health concern associated with the medicated feed may be identified through the reportable food registry, recalls, consumer complaints, or other means.

2. Pre-Approval Inspections (Priority 2)

Conduct pre-approval inspections of firms applying for an Original medicated feed mill license. The inspection is required to take place before a medicated feed mill license is approved and should take place within 60 days of the filing of a license application. FDA has a 90-day statutory obligation to act on a license application (21 CFR § 515.20 and § 512(m)(2) of the FD&C Act).

3. Assignment List (Priority 3)

Inspect the facilities indicated in the work plan assignment as being the highest priority. As always, re-inspect firms on the list whose most recent inspection was classified Official Action Indicated (OAI) within 180 days. Additionally, you should re-inspect an OAI firm within 180 days of issuing the firm a Warning Letter to determine if CGMP violations have been corrected. Prior to conducting OAI follow-up inspections the OHAFO division should consult with CVM to discuss strategy and focus.

B. Inspection Types

1. Comprehensive (e.g., Surveillance) Inspection

The primary purpose of a comprehensive inspection is information gathering. There is no reason to believe that there are any problems based on prior history or, in the case of the initial inspection of an establishment, lack of inspectional history.

Conduct comprehensive inspections of firms where CVM or the firm has requested pre-approval inspection (Priority 2) and where firms are scheduled for inspection (Priority 3). Comprehensive inspections may become more focused and similar to a directed (e.g., compliance or for-cause) inspection when conditions are uncovered during the comprehensive inspection that show:

(1) that there is a potential for causing unsafe drug residues in food animals,

(2) that adverse health consequences in animals fed the medicated feed have occurred or may occur,

(3) where there is a reasonable potential for adversely affecting the safety or other characteristics of the finished animal food,

(4) the firm is not able to demonstrate compliance with, or a good understanding of, the CGMP regulations and their intent; or,

(5) the investigator has identified significant non-compliance with required medicated feed labeling.

If the comprehensive inspection uncovers these types of issues, consult with the CVM and the OHAFO division to determine how to focus the inspection to potentially support a compliance action.

2. Directed (e.g., For Cause) Inspection

A directed inspection is based on information suggesting that there may be a significant problem

or that there actually has been a significant problem that should have been corrected. This information could be the result of sample analyses, prior inspection, recall, comprehensive (e.g., surveillance) inspection, or other information received by the OHAFO division. Conduct directed inspections (Priority 1) of those firms with a significant violative history, those firms involved in a violative tissue residue report as well as other adverse events.

There are no specific surveillance sample collections planned for these inspections. Contact CVM at CVMAnimalFoodPrograms@fda.hhs.gov before collecting any "for cause" samples if egregious adverse conditions exist during an inspection. **Note: Place "Medicated Feed For Cause Sampling" in the subject line of the email**.

3. State Contract Inspections

For State contract inspections, refer to the annual contract statement of work.

C. Program Interactions

Refer to Compliance Program 7371.005, Type A Medicated Articles, for guidance on firms that manufacture Type A Medicated Articles. Time should be charged accordingly.

Refer to Compliance Program 7371.009, BSE/Ruminant Feed Ban Inspections, for guidance on inspections/investigations of renderers, protein blenders, licensed and non-licensed medicated feed firms, animal food facilities, distributors, retailers, on-farm mixers, and ruminant feeders. Time should be charged accordingly.

Refer to the current fiscal year Preventive Controls for Animal Feeds (PCAF) Inspection work plan assignment for guidance on inspections/investigations of firms that are subject to 21 CFR part 507, Current Good Manufacturing Practice, Hazard Analysis, and Risk-based Preventive Controls for Food for Animals. For additional guidance on conducting inspections at facilities subject to 21 CFR part 507, please review Guidance for Industry #235: Current Good Manufacturing Practice Requirements for Food for Animals as well as Guidance for Industry #245 Hazard Analysis and Risk-Based Preventive Controls for Food for Animals (Draft).

Facilities that are required to register under section 415 of the FD&C Act that are also manufacturing, processing, packing, or holding medicated feed must comply with both 21 CFR part 225 and 21 CFR part 507, unless an exemption applies. For example, if a medicated feed firm manufactures both non-medicated feed and medicated feed, its production of non-medicated feed is subject to 21 CFR part 507, and its production of medicated feed is subject to 21 CFR part 225 and part 507. Farms exempt from 21 CFR part 507 that manufacture medicated feed are still required to comply with 21 CFR part 225. Firms that are considered a very small business, are only subject to a portion of 21 CFR Part 507 if they submit a qualified facility attestation, please refer to the current year fiscal PCAF assignment for more information.

We recognize that in many instances medicated feed firms will be using the same building, grounds, employees, supervisors, management, equipment, and utensils to perform operations under 21 CFR part 507 and part 225. In instances where the medicated feed firm is subject to both

21 CFR parts 225 and 507 and the CGMPs overlap, the medicated feed firm must follow the more specific requirements found in 21 CFR part 507. For example, there are similar requirements in part 225 and part 507 for personnel qualifications, training, and supervision. However, the requirements in part 507 are more specific in how to meet these requirements. The medicated feed firm must ensure that they are in compliance with these more specific requirements in part 507.

As a reminder, the CGMPs under 21 CFR part 507, subpart B do not address the use of animal drugs in the manufacturing of medicated animal feed. Therefore, the medicated feed firm must also follow the specific requirements in 21 CFR part 225 related to the use of drugs in the manufacture of medicated animal feed, such as provisions for the handling of drugs and medicated mixes and for laboratory controls. For facilities that are required to comply with the PC requirements, they may consider practices that they use to meet the requirements in 21 CFR part 225, such as sequencing, flushing, and drug inventory and control procedures (i.e. batch records), in their hazard analysis to determine if a drug, or drug carryover hazard requires a preventive control.

In addition, when conducting an inspection at facilities that are subject multiple CVM program areas such as 21 CFR part 507 and 21 CFR 225, you must conduct a comprehensive inspection and ensure all program areas and PAC codes are covered during that inspection.

PART III - INSPECTIONAL

1. Inspectional Operations

An important responsibility of all animal food firms is to ensure that the animal food produced, whether medicated or non-medicated, is truthfully labeled, does not contain unsafe additives or contaminants, and, if drugs are present, they are safe and effective for their intended approved use, alone or in combination. Medicated feed should be properly mixed according to the drug approval and the medicated feed CGMPs to ensure medicated feed manufactured is safe, has labeled identity and strength, and meets quality and purity characteristics it should possess with respect to its drug content.

General inspectional procedures should be followed during a medicated feed inspection, such as applicable field bulletin and IOM procedures. The main focus for the Medicated Feed Manufacturing Compliance Program is the inspectional and regulatory coverage of medicated feed firms to determine if they are in compliance with the regulatory requirements (including CGMP and VFD requirements).

All firms manufacturing, processing, packing, or holding animal food (medicated and non-medicated) for consumption in the U.S. should be registered as a food facility, unless an exemption (21 CFR § 1.226) applies. In addition to the requirements in 21 CFR part 507, firms planning to manufacture medicated feeds that require a medicated feed mill license must comply with the requirements of 21 CFR part 515 and 21 CFR § 225.10 - 225.115, and be registered as a drug establishment in accordance with 21 CFR part 207. Firms planning to manufacture

medicated feeds that do not require a medicated feed mill license must comply with the requirements of 21 CFR § 225.120 – 225.202, as well as 21 CFR part 507. FDA determines whether a medicated feed firm is complying with the requirements of the CGMP regulations by inspecting the firm's controls, operations and facilities at periodic intervals. Registered drug establishments are to be inspected on a risk-based schedule.

A. CGMP Information

1. Comprehensive (e.g., Surveillance) Inspections

Comprehensive inspections are conducted to determine whether a firm is in compliance with applicable CGMP requirements, or whether voluntary action by the facility or official action by FDA is necessary. Overall compliance is determined by review of certain portions of the firm's operations using Form FDA 2481 as a guide to recording observations and evaluating licensed medicated feed CGMP compliance. With the exception of the identifying firm data, the remainder of the FDA 2481 refers to the licensed medicated feed CGMPs (21 CFR § 225.10-225.115), and is not for use in inspecting non-licensed or non-medicated feed firms.

EACH "NO" ANSWER ON THE FORM FDA 2481 SHOULD BE FULLY EXPLAINED (AND DOCUMENTED, IF POSSIBLE) IN THE NARRATIVE SECTION. ITEMS NOT COVERED ON THE FORM FDA 2481 SHOULD BE MARKED AS N/C (NOT COVERED). Documentation can be accomplished by various means such as collection of photocopies of the records in question, photography, sample collection, obtaining of affidavits, etc. Also, reading the IOM about photography and the associated explosion hazards is highly recommended.

The key licensed medicated feed CGMP elements are designated on Form FDA 2481 with an asterisk. All items on the checklist are to be covered. However, greater importance should be placed on the asterisked items. These items should be addressed and adequately documented in the narrative portion of the form to enable the OHAFO division reviewer to classify the inspection and determine appropriate monitoring and follow-up at the firm.

During comprehensive inspections, a suggested inspectional approach is to select at least two drugs (at least one Category II, Type A medicated article) and trace these drugs through the system, from receipt to distribution of the medicated feed. Public health risk should be considered when choosing the drugs to trace. Some risk factors to consider include, outside of Category II, Type A medicated articles, could be whether they have elevated risk concerns for other species (e.g., monensin in a facility the produces horse feed), or whether it is a complex formulation or manufacturing process (e.g., liquid or free choice feeds). Determine if the establishment can (1) trace forward and recall its product, and (2) can trace back the medicated article or the medicated feed received from its suppliers.

2. Pre-approval Inspections

New applicants may be newly constructed or acquired facilities, or active medicated feed firms that wish to secure a license. When a firm applies for a medicated feed mill license, CVM will request the OHAFO division conduct a pre-approval inspection. The investigators performing

these inspections determine whether the firm has the necessary knowledge of CGMP requirements, adequate equipment, drug receipt and inventory controls, formula and production instructions/records, and sampling and assay plans to demonstrate their ability to comply with the CGMP requirements for licensed feed mills (21 CFR § 225.10 - 225.115).

At the time of a pre-approval inspection, the feed mill is only legally required to comply with the CGMP regulations that apply to non-licensed facilities (21 CFR § 225.120 - 225.202). If the Investigator observes deviations from the CGMPs applicable to non-licensed facilities, the Investigator can document these on a Form FDA 483. Deviations from the CGMPs that apply to licensed facilities should not be documented on a Form FDA 483 during a pre-approval inspection.

The goal of a pre-approval inspection is to determine if a firm is capable of complying with the licensed feed mill CGMPs. Although a firm does not have to currently be compliant with these CGMPs, they should be able to demonstrate their knowledge of and ability to comply with the more stringent requirements of the licensed feed mill CGMP regulations. Some examples of a firm demonstrating their knowledge and ability to comply during the FDA inspection include:

- Having licensed feed mill procedures already created and implemented in daily operations.
- Having licensed feed mill procedures created and ready to be implemented.
- Discussing with the investigator, in detail, the procedures that will be created and implemented.

When a firm is not in compliance with the non-licensed feed mill CGMP requirements during a pre-approval inspection, notify the CVM before the OHAFO division recommends a refusal to approve the medicated feed mill license. Additionally, if major and critical deviations from the non-licensed CGMP regulations are observed during a pre-approval inspection, the Agency may consider follow-up enforcement action. (see V.5. Administrative/Regulatory Sanctions)

3. Directed (e.g., Compliance) Inspections

Directed inspections are conducted to evaluate a firm's compliance with the provisions of the CGMP regulations and to document inspectional observations supporting possible enforcement action.

Directed CGMP inspections are to be conducted at firms where previous CGMP inspections have been classified by the OHAFO division office as OAI (District Decision Data Code “A”) or firms that have had an adverse event.

Also, Comprehensive “Surveillance” inspections may be converted to Directed CGMP inspections upon observation of violations as outlined earlier in Part II. 2. B.

4. Registration and License Status

Item 3, Medicated Feed Inspection Report (Form FDA 2481)

Review the medicated feed firm's drug establishment registration and license status. A firm's drug establishment registration information may be found on the Drug Establishments Current Registration Site. A firm's medicated feed mill license status may be found on the Medicated Feeds web page.

Food Facility Registration as required under the Bioterrorism Act.

- If a firm is not registered as a food facility and is required to register as a food facility, provide them with information about how to register. Remind them that food facility registration is required to be renewed biennially.

Drug Establishment Registration and Medicated Feed Mill License

In order to manufacture with a Category II Type A medicated article, a firm is required to be registered as a drug establishment and required to hold an approved medicated feed mill license.

- Provide the firm with information about how to register as a drug establishment, Resources for Registering. Remind them that drug establishment registration is required to be renewed annually between October 1 and December 31.

- Provide the firm with information on where to find the Medicated Feed Mill License application (Form FDA 3448). The application is available as a fillable PDF but will need to be submitted in hard copy with an original signature to CVM via USPS (FDA/CVM, Division of Animal Feeds, HFV-220, 12225 Wilkins Avenue, Rockville, MD 20852).

Drug Establishment Registration Cancellation and Medicated Feed Mill License Voluntary Withdrawal

Provide the form letter (Attachment B**)** to a firm to withdraw its medicated feed mill license without prejudice. Forward to the completed letter to CVM's Division of Animal Feeds (HFV-220), via email (MedicatedFeedsTeamMail@fda.hhs.gov) or USPS (FDA/CVM, Division of Animal Feeds, HFV-220, 12225 Wilkins Avenue, Rockville, MD 20852).

Inform the firm to electronically withdraw (De-Registration) their drug establishment registration.

A link to the registration portal can be found on the FDA website at:
https://www.fda.gov/animal-veterinary/animal-food-feeds/medicated-feeds

5. CGMP Guidance

Some background information as well as interpretation of licensed medicated feed CGMP regulations for the asterisked items in the Form FDA 2481 is listed below. Numbers in parenthesis refer to the applicable section and paragraph of Title 21 CFR where the requirement is located. An asterisked item in the Form FDA 2481 is a CGMP element for which non-

compliance is likely to have a significant negative impact on the safety of the manufactured medicated feed and public health. (21 CFR part 225)

Subpart B - Construction and Maintenance of Facilities and Equipment

Equipment (§ 225.30)

Asterisked Item 25

All equipment, including scales and liquid metering devices, shall be of suitable size, design, construction, precision, and accuracy to make accurate measurements of the critical animal food components. All scales and metering devices shall be tested for accuracy upon installation and at least once per year subsequent to that installation, or more frequently as may be necessary to insure their accuracy. Inaccurate measuring devices can significantly affect the potency of the finished medicated feed. Review scales and metering devices' calibration records, or request that the firm demonstrate the accuracy of these devices.

Use of work areas, equipment, and storage areas for other manufacturing and storage purpose (§ 225.35)

Asterisked Item 30

Work areas and equipment used for the manufacture or storage of medicated feeds or components thereof shall not be used for, and shall be physically separated from, work areas and equipment used for the manufacture of fertilizers, herbicides, insecticides, fungicides, rodenticides, and other pesticides unless such articles are approved drugs, indexed drugs, or approved food additives intended for use in the manufacture of medicated feed. Manufacture, use, or storage of these other products in areas where medicated articles, medicated feed, or animal food are used or stored can significantly increase the risk of adulterating medicated feed. Capture in the EIR, or an affidavit if appropriate to support an action, what their procedures and practices are to avoid the adulteration of medicated articles, medicated feed, or animal food with these types of products.

Subpart C - Product Quality Control

Drug Components (§ 225.42)

Asterisked Item 40

Type A Medicated Articles, medicated premixes, and semi-processed (i.e., intermediate premixes, in plant premixes, and concentrates) intermediate mixes containing drugs shall be properly identified, stored, and handled in a manner to prevent mix-ups and contamination that may adversely affect the identity, strength, quality, or purity of the drug (e.g., includes leakage and or breakage of bagged Type A medicated article or medicated feeds). Failure to adequately identify, store, handle and control drug components could cause serious defects in finished medicated feed, and could adversely affect animals and humans consuming the edible products thereof. Capture in the EIR, or an affidavit if appropriate to support an action, the firm's practices and observe

how these drug components are identified, stored, and handled to ensure there is consistent and accurate identification and use.

Asterisked items 45 and 47

A firm must establish and maintain a daily inventory record for each drug used. This record is required to show when and which drug lot was used in specific batches or production runs of medicated feed; how much was used; and how much remains in inventory after each daily use in order to cross-check drug usage with production records. These are critically important elements. The term "daily" means each 24-hour period that a drug component is used. The inventory records are intended to serve a useful quality control function to detect errors in drug usage. Any significant discrepancy shall be investigated and corrective action taken. The medicated feed(s) remaining on the premises which are affected by this discrepancy shall be detained until the discrepancy is reconciled. The inventory record may be several records that interrelate to provide the needed information. This record shall be maintained on the premises for at least one year after complete use of a drug component of a specific lot number or feed manufacturer's shipment identification number. An individual at the manufacturing site should be able to demonstrate how the record keeping system works. Capture in the EIR, or an affidavit if appropriate to support an action, how the inventory is conducted and what is done when a discrepancy is noted. For additional guidance see Compliance Policy Guide (CPG) Section 680.200.

Laboratory Controls (§ 225.58)

Asterisked item 51

The firm's assay procedures and sampling schedules shall conform to license requirements, 225.58(b)(1), which require at least three representative samples of medicated feed containing each drug or drug combination be collected and assayed by approved official methods, at periodic intervals during the calendar year, unless otherwise specified. When a feed mill starts using a drug they have not previously used, at least one of these assays shall be performed on the first batch that the feed mill manufactures using the drug. In subsequent years the three assays may be distributed throughout the year (e.g., it is not necessary that the feed mill assays the first batch each year, they can randomly select three batches throughout the year). Review all of the assays conducted within the last year to ensure that all the required assays have been performed and that all the assays that have been performed are within the specified limits. (see 21 CFR § 558.4(d) for the assay limits)

If a medicated feed contains a combination of drugs, only one of the drugs needs to be analyzed each time, provided the one tested is different from the one(s) previously tested. An exception is made for a medicated feed manufactured from a fixed combination Type A Medicated Article. One or all of the drugs in a fixed combination may be analyzed and if one or more drugs analyzed meets specifications, then the medicated feed is considered to be in specification. If only one drug is analyzed in the fixed combination, the other drug(s) do not have to necessarily be analyzed in future samples; that is, the same marker drug can be used each time an assay is performed.

Asterisked items 52 and 55

Analysis of medicated feed provides some measure of performance of the manufacturing process. When the results of sample analysis reveal that a drug level in a batch of medicated feed is out of specification, adequate investigation and corrective action shall be undertaken by the firm to comply with 225.58(d) and (e). Such investigation shall be documented and the record of such action must be maintained on the premises. Corrective action shall include provisions for discontinuing distribution where the medicated feed fails to meet the labeled drug potency. Distribution of subsequent production of the particular feed shall not begin until it has been determined that proper control procedures have been established.

Adequate investigation and corrective action would include a recheck of the critical manufacturing steps. For example:

- Examine the daily drug inventory records to determine whether the correct Type A Medicated Article and level was used.
- Verify formula for correct Type A Medicated Article, potency, and use level.
- When appropriate, check for incorrect codes that were applied by the firm to the Type A Medicated Article.
- Check for production yields of target, preceding, and subsequent batches.
- Depending upon the nature and precedence of a drug assay problem, the firm may choose to assay a split portion of the sample, assay the Type A Article, and/or review the problem with the Type A Article manufacturer.
- Determine whether proper control procedures were followed.
- Place current inventory from target batch on hold and cease production of target animal food pending conclusion of investigation. If the target batch has been distributed the firm may consider a recall strategy.
- Did firm initiate recall?

One of the reasons for conducting an investigation following an out of limits assay is to determine whether or not a manufacturing error has taken place. Assays are considered a check on procedures and controls, and unexpected and/or extreme findings may indicate a serious problem. Repeated instances of out of limits assays of the same drug for sampling, handling, and method performance should be investigated further and require additional corrective action, since the expectation is that out of specification drug levels would not be a routine occurrence.

The firm must have a written record of the complete investigation and all analytical results, the conclusion reached, and the action taken. Review the record to determine if the samples were analyzed as required, whether the investigation was complete, if any remaining medicated feed from the batch was held pending completion of the investigation, and whether the conclusion and action appears appropriate. All out of limits assays for medicated feeds along with the subsequent investigation and resolution should have been reported to CVM (HFV-220) per 21 CFR part 510.301. These reports should be sent via USPS to FDA/CVM, Division of Animal Feeds, HFV-220, 12225 Wilkins Avenue, Rockville, MD 20852.

Equipment Clean-out Procedures (§ 225.65)

Asterisked item 32

The firm must have adequate cleanout procedures for all equipment used in the manufacture and distribution of medicated feeds to prevent unsafe carry-over of drugs into subsequent production of animal food. These procedures may consist of physical means such as vacuuming, sweeping, washing, etc. Flushing and physical clean-out are two commonly used equipment clean-out procedures. Sequencing (ordering the batches of medicated feed in a way that does not result in adulterated animal food) is commonly used to prevent the need for flushing or a physical clean-out between certain batches of feed.

Determine whether the firm's standard operating procedures appear adequate to prevent unsafe carry-over of drug residues and whether the firm follows the written procedures. Ask whether the firm follows the same procedures for all batches of medicated feeds, or whether it depends on the feed being produced. Also, capture in the EIR, or an affidavit if appropriate to support an action, how they determined that their cleanout procedures are effective in preventing unsafe contamination of animal food. If the adequacy of the firm's clean-out procedures is questioned, follow CPG 680.500, Unsafe contamination of Animal Feed from Drug Carryover.

Flushing is the process of using an ingredient, usually an abrasive-type material such as corn, soybean meal, peanut hulls, etc., after the production of a batch of medicated feed, through the manufacturing equipment and associated handling equipment (e.g., conveyors) for the purpose of cleaning out any drug residue. The flush material must be properly identified, stored, and used in a manner to prevent unsafe contamination of other feeds. If the firm uses a flushing procedure to prevent unsafe carry-over, determine and report how the firm has established the kind and quantity of flush material to be used. In addition, report how the flush materials are used, recovered, stored, and identified for subsequent use. If there is potential that use of flush materials may result in unsafe contamination of animal food, include the observation on the Form FDA 483 (see CPG 680.500 for guidance).

Physical clean-out of medicated feed mixing and handling equipment is typically a dry type cleaning such as vacuuming, sweeping, or scraping. The regulation also provides for washing; however, due to other animal food and environmental safety questions and concerns, washing is not generally utilized.

Sequencing is a preplanned order of production, storage, and distribution of different animal feeds designed to direct drug carryover into subsequent feeds which will not result in unsafe contamination. (see CPG 680.600, Sequencing as a Means to Prevent Unsafe Drug Contamination in the Production, Storage, and Distribution of Feeds) Sequencing should be based upon a valid rationale to prevent unsafe contamination in subsequently produced animal food. For instance, a sequencing procedure that allows for mixing a swine finishing ration after a medicated feed containing sulfamethazine is not acceptable, since it has been shown that a very low concentration of sulfamethazine consumed up to slaughter can result in illegal residues in edible tissues. It is also unacceptable to mix animal food for a horse subsequent to mixing a monensin or lasalocid-containing animal food due to severe or fatal effects of these drugs in horses. Capture in the EIR, or an affidavit if appropriate to support an action, how the firm handles interruptions to their sequencing schedule e.g., do they perform a flush after an

unscheduled batch of medicated feed.

Subpart D - Packaging and Labeling

Blue Bird Labels

Blue Bird labels serve as the source of information that must appear on the actual medicated feed labels. In accordance with 21 CFR § 515.10(b)(7) licensed medicated feed manufacturers have committed as part of their application that the feed manufacturing facility will be in the possession of current approved or index listed Type B and/or Type C medicated feed labeling for each Type B and/or Type C medicated feed to be manufactured prior to receiving the Type A medicated article containing such drug. Ask whether the manufacturing facility has the Blue Bird label on the premise, or whether they have it available electronically by computer or obtaining a copy by facsimile. In assessing compliance with the requirement in 21 CFR § 515.10(b)(7), consider the firm's overall ability to generate accurate medicated feed labels (see item 65d on Form FDA 2481). Approved Blue Bird labels are available at Animal Drugs @FDA.

Labeling (§ 225.80)

Asterisked items 61 and 62

Labeling (including placards and invoices when used in lieu of bag labels) must contain adequate directions and warnings for the safe and effective use of medicated feeds. Labels and labeling shall be handled (received, printed, stored, and/or applied) in a manner that prevents labeling mix-ups and assures that correct labeling is employed for the medicated feed. If the firm receives labels and labeling from a printing company, these labels and labeling must be proofread upon receipt from the printer against the Master Record File to verify their suitability and accuracy. The proofread label shall be dated, initialed by a responsible individual, and kept for 1 year after all the labels from that batch have been used. Label stock shall be reviewed periodically and discontinued labels shall be discarded. If the firm stores their labels and labeling electronically and prints on site ask about their procedures to ensure adequate handling. Capture in the EIR, or an affidavit if appropriate to support an action, how they handle electronic files, who has access to alter those electronic files, and how they ensure the correct label or labeling is printed and applied. When medicated feeds are distributed in bulk, complete labeling shall accompany the shipment and be supplied to the consignee at the time of delivery.

Check labeling for proper withdrawal times (verify using label of approved NADA). Determine whether mixer-feeders are knowledgeable of and following proper withdrawal times. If there are discrepancies with the labeling, check to see if the Blue Bird labels are accessible.

Subpart E - Records and Reports

Master record file and production records (§ 225.102)

Master record files provide the complete procedure for manufacturing a specific product, setting forth the formulation, theoretical yield, manufacturing procedures, assay requirements, and labeling of batches or production runs.

Item 64

Some firms develop/amend their animal food formulas at one location and transmit them via computerized systems to a number of animal food manufacturing facilities. Most of the time, it has been difficult for the investigator to verify that each master file record has been checked, dated, and signed or initialed by a qualified person. When this scenario is encountered, mark **item 64** "No", indicating why in the narrative section. Although this is a non-asterisked item, the information should be provided in the EIR for possible inspection of the site that develops/amends the formulas.

Asterisked item 65

Many firms do not continue to maintain traditional hardcopy Master Record Files. Most of these records are maintained electronically as parts of other records or files. Verify compliance by ensuring the firm has all the components required by this section either stored together or in separate files. Failure to comply with the minimum master file requirements could result in production of medicated feeds which do not meet specifications.

Asterisked item 70

Production records provide a complete batch history that can be compared to the Master Record File to ensure a medicated feed has been properly manufactured. The production records can also be used to investigate possible issues and provide ingredient traceback in the event of a problem with a medicated feed.

Distribution records (§ 225.110)

Asterisked item 81

Distribution records must contain enough information to enable the manufacturer to trace specific batches of medicated feeds should there be any question regarding drug safety or efficacy e.g., complaints, recalls, etc. Distribution records for each shipment of a medicated feed shall include the following:

1. The date of shipment,
2. The name and address of purchaser,
3. The quantity shipped,
4. The name of the medicated feed,
5. A lot or control number, or date of manufacture or other suitable identification

Request to review distribution records. Ask if the firm has ever had to recall or recover a medicated feed for quality or safety reasons. If so, determine whether they were able to effectively do so using their distribution records.

B. Veterinary Feed Directive Drugs (VFD)

1. Requirements:

Inspections of feed mills should determine compliance with the requirements for production and distribution for use of VFD drugs found in 21 CFR § 558.6. Ancillary inspections may extend to animal producers, non-licensed feed mills, and to veterinarians when following or tracing the use of VFD feed.

A distributor is defined as "any person who distributes a medicated feed containing a VFD drug to another person. Such other person may be another distributor or the client-recipient of a VFD." A "person" can be an individual or business entity. If the same person is both (1) distributing VFD feed and (2) acting as the client in the context of the VCPR that the VFD order has been authorized under, then the person is not distributing VFD feed to another person and is not a distributor. If different people are doing both things, then the person distributing the VFD feed is distributing VFD feed to another person and is therefore a distributor within the context of the VFD rule.

The distributor and the client must retain a copy of the VFD order for 2 years. In addition to other applicable recordkeeping requirements found in 21 CFR § 558.6, if the distributor manufactures the animal food bearing or containing the VFD drug, the distributor must also keep VFD feed manufacturing records for one year in accordance with 21 CFR part 225.

In order to distribute VFD feed, a distributor must have either a lawful VFD order or an acknowledgement letter from another distributor (see Definitions). In the case of transfers of VFD feed between two locations of the same corporate entity we would not consider the corporate entity to be distributing to another person. Therefore, an acknowledgment letter would not be required for transfers within the same corporate entity.

A distributor of VFD feed is required to notify FDA prior to the first time it distributes VFD feed. Distributor notification must include the distributor's complete name and business address; the distributor's signature or the signature of the distributor's authorized agent and the date the notification was signed.

Those who wish to distribute VFD feeds (21 CFR § 558.6(c)(7)) must notify in writing FDA/CVM of their intent to distribute at the following:

Food and Drug Administration
Center for Veterinary Medicine
Division of Animal Feeds (HFV-220)
12225 Wilkins Avenue
Rockville, MD 20852

or via facsimile at (240) 453-6882

Distributors must also notify FDA within 30 days of any change in ownership, business name, or business address.

Listings of Veterinary Feed Directive Distributor Notifications can be found at Animal Drugs @FDA.

For multiple locations, each address must be included in the notification. A firm with multiple locations can send separate VFD distributor notifications for each location, or they can submit one letter stating their intent to distribute VFD feeds at each of their locations, including each location's physical address. Both would be acceptable as long as they contain the required information mentioned above.

For further information see the VFD web page.

2. Inspectional Guidance:

Formerly, Form FDA 2481 included a section on VFDs. This section has been reserved for future inclusion of updated VFD questions in the current version of Form FDA 2481, and any previous versions of this form should not be used. The new VFD Inspection Tool (provided as a fillable PDF) that is distributed with the VFD work plan assignment contains updated questions similar to the types of VFD questions that used to be on the Form FDA 2481. When directed to as part of a VFD assignment, the VFD Inspection Tool should be used in order to obtain inspectional data about compliance with the VFD requirements. Use the VFD Inspection Tool as a guide to recording observations and evaluating compliance with the VFD requirements for medicated feed firms manufacturing or distributing VFD feed.

If firms handle VFD drugs, audit the paper trail (e.g., the VFD or acknowledgment letter, the batch records, and distribution records) for at least one VFD feed manufactured by the firm. Records for VFD orders should be checked to determine compliance with the VFD distribution regulations.

Compare either the VFD or the acknowledgement letter with the VFD order and distribution records of VFD feed to ensure that the VFD or acknowledgement letter requirement was met. During review of production records verify the disposition of any overrun or leftover VFD feed. As with any drug used in medicated feed, attention should be given to labeling to assure proper directions and cautions are included. Questions concerning the VFD requirements are addressed in Guidance for Industry (GFI) #120. Fully document any deviations from VFD recordkeeping requirements and describe in the EIR and VFD Inspection Tool. Refer to the current fiscal years' VFD work plan assignment memo for additional information.

The VFD Inspection Tool also incorporates questions on how the veterinarian and client comply with the VFD rule. The investigator should choose one VFD to trace back to the veterinarian authorizing the VFD and trace forward to the client using the VFD feed in order to complete these questions. During the course of a medicated feed mill inspection this "trace back" to the veterinarian and "trace forward" to the client would be virtual through the feed mill's records -- we do not intend the person doing the medicated feed CGMP inspection to pay a visit to the veterinarian and client. Instead we would want to look at the distribution record (or other record) that demonstrates how the VFD order is received, and how the finished feed is distributed.

C. Other Non-CGMP Issues

1. Manufacture of Medicated Feed Without The Required Feed Mill License

If a feed mill does not have an approved medicated feed mill license but has a Type A medicated article requiring an approved medicated feed mill license in its drug inventory for mixing the drug into medicated feed is a violation that may warrant advisory or enforcement action. The Investigator should fully document the receipt and use of a medicated article requiring a medicated feed mill license and/or distribution of a medicated feed (21 CFR § 558.4). Contact your OHAFO division management and CVM to discuss the violative situation.

Document information of the shipper of the Category II Type A medicated article. The shipper of the Type A medicated article may have caused the drug to be unsafe if the receiver and user do not have the required approved medicated feed mill license for such use (Section 512(a)(1) of the Act). After consultation with the OHAFO division and CVM, it may be appropriate to perform a follow-up investigation at the shipper to determine their practices of distributing drugs requiring approved medicated feed mill licenses. Complete documentation of the responsibility and the violation may support advisory or enforcement action against both the consignee/user and the shipper/distributor. Document (e.g., affidavits, freight bills, receiving tickets, etc.) shipments of Type A medicated articles requiring an approved medicated feed mill license from the distributor to unauthorized consignees, including the consignee/user mill just inspected.

The manufacture of medicated feed without the required feed mill license and drug establishment registration may warrant an official response. The manufacture of a medicated feed that requires a license without a medicated feed mill license results in the medicated feed being considered unsafe. (Section 512(a)(2)(B) of the Act). A drug or medicated feed that is considered unsafe is considered adulterated. (Section 501(a)(5) and 501(a)(6) of the Act).

2. Unapproved Drugs used in Medicated Feed

The manufacture of medicated feed without required approvals, with illegal combinations, or from unapproved sources of drugs are violations that may warrant advisory or enforcement action. Fully document the mixing and distribution of unapproved drugs or the manufacture and distribution of medicated feed containing unapproved combinations of new animal drugs. The Agency's extra-label use policy does not apply to the manufacture of medicated feed because extra-label use of drugs in or on animal feed is not permitted (21 CFR § 530.11(b)). For information regarding extra-label use of medicated feed in minor species see CPG 615.115, Extra-Label Use of Medicated Feed for Minor Species.

If a medicated feed mill license applicant manufactures unapproved medicated feed, the license approval shall be refused. (see 21 CFR § 515.21(a)(3)). If a licensed feed mill manufactures unapproved medicated feed and does not discontinue that manufacturing within a reasonable time, then it shall be considered as a reason to revoke the license. (see 21 CFR § 515.22 (c)(4)).

3. Prescription Drugs

Be alert for possible sales of prescription animal drugs, particularly drugs administered in drinking water, and determine whether these drugs are dispensed through a person lawfully filling the order (e.g., veterinarian, licensed pharmacist, etc.) on the prescription order of a licensed veterinarian. Many of these drugs that were previously available over-the-counter transitioned to prescription status on January 1, 2017 (see List of Approved New Animal Drug Applications

Affected by Draft GFI #263). This does not include VFD drugs. Note: VFD drugs are not prescription drugs.

2. Import Operations

Entry review

Entry review supporting materials, including initial admissibility requirements, can be found on the *CVM Import Resources* page in the *Initial Admissibility Resources* section located on the FDA intranet (see http://inside.fda.gov:9003/ora/offices/oeio/importprogram/commodityresources/ucm556362.htm).

For instructions on reporting time for entry review refer to OEIO-IMP-PCC-SOP.002 Import Entry Review Time Reporting.

Report time solely under PAC 71004 for label examinations. A label should include, but is not limited to, the name of the medicated feed, indication(s) for use, active drug ingredient(s), guaranteed analysis, ingredients, mixing directions, caution statement, warning statement, manufacturer information, weight statement, and other information such as lot/batch number, expiration date and any other information as required under the NADA approval. For additional information, refer to the *Guidance for Industry #181 Blue Bird Medicated Feed Labels* and Subpart D, Packaging and Labeling, above.

For questions regarding a specific label examination, contact: CVMImportRequests@fda.hhs.gov.

Sample collection

Routine surveillance sampling is not indicated under PAC 71004, unless directed by a CVM assignment or other directive from CVM. Sampling may be indicated under other CVM compliance programs (e.g., BSE and Feed Contaminants Compliance Programs).

3. Official Samples

The collection of evidence to demonstrate and document violations is a necessary element for an enforcement action. For judicial actions (e.g., injunction, seizure, warrant, prosecution), a documentary sample of interstate commerce records should be collected for each violative asterisked item on Form FDA 2481. For advisory or enforcement action (e.g., untitled letters, warning letters), the same information should be collected and attached to the EIR, but does not need to be submitted as a documentary sample. See Field Alert #40.

When necessary to document violations, the primary type of samples taken during medicated feed inspections should be documentary samples. Documentary samples efficiently illustrate the violative situation and provide adequate evidence for enforcement action.

The OHAFO division should contact CVM Compliance, HFV-230 if they are considering

collecting a physical sample of medicated feed to document violations, such as residue carry-over, drug potency or cross contamination. If a physical sample is being collected, the following instructions pertain:

- For bagged complete animal food:
  Collect a total sample of not less than 2.3 KG (5 lbs.) from each lot. Collect 454 grams (1 lb.) subs, sampling all available bags from lots of 10 bags or less. If the lot size is greater than 10 bags, collect 454 grams (1 lb.) from each of 10 bags selected at random.

- For bulk complete animal food:
  Collect at least 10 bags of 454 gram (1 lb.) subs from different points in the bulk lot to obtain a minimum total sample of 4.5 kg. (10 lbs.)

- For Investigational (INV) Samples, collect at least 900 grams (2 lb.) of static residual material from the manufacturing equipment and correlate these with finished animal food samples. Please contact CVM prior to collecting an INV sample.

Note: Contamination not related to drug use should be covered under the Feed Contaminants Compliance Program 7371.003.

A. General Sampling Guidelines/Additional Information

See the current IOM sampling schedule that pertains to medicated feed for sample sizes, potency and drug carry-over determinations in animal food, etc.

When sampling animal food, it is important to adhere to the following guidelines:

- When sampling bagged complete animal food, insert the trier the full length of the bag. Clean the trier between sampling different lots of complete animal food.
- Collect potency samples and cross-contamination samples in whirl-pak plastic bags. DO NOT USE PAPER BAGS. STORE IN ACCORDANCE WITH LABEL INSTRUCTIONS.
- DO NOT fumigate samples intended for potency analysis, drug carry-over or cross contamination analysis.
- Always store product according to label instructions.

B. Medicated Feed Mill Sample Preparation and Shipment

Submit FDA samples to the Denver Laboratory (DENL) with a copy of the product labeling. Bulk or retail labeling is critical for potency determination and is helpful for contaminant analysis Samples should be analyzed both for antibiotics and other drugs. Telephone the Denver Lab prior to shipment at 303-236-9651; refer to the current IOM for contact information updates. Address samples to:

Food and Drug Administration
6th and Kipling St.
Building 20
Denver Federal Center
Denver, CO 80225-0087

PAC 71004
PAF: ANT (ANTIBIOTICS IN FOODS AND FEEDS)
Note: any PAC or PAF related issues, please direct your questions to ORA/ORS

State officials should submit their samples to the appropriate State laboratory unless instructed otherwise.

PART IV - ANALYTICAL

1. Analyzing Laboratories

FDA Laboratories - All analyses will be done by Denver Laboratory (DENL).

State Laboratories - State laboratories will prepare and analyze their own samples unless instructed otherwise.

2. Analysis

Sample Analysis

Conduct all analyses for potency on the composite portion before analyzing individual subs, as needed. Analysis for drug carry-over is to be done on individual subs.

Analyze individual subs only when results on individual subs are deemed necessary to support advisory or enforcement action. In general, analyze a minimum of five subs to demonstrate degree of sample homogeneity.

Drug Contaminant Analysis

Questions concerning the technical or scientific aspects of analysis should be directed to the Office of Regulatory Science, 301-796-6600. Questions concerning regulatory action levels or potentially hazardous levels should be directed to CVM, Division of Compliance, HFV-230, 240-402-7001, CVMCompliance@fda.hhs.gov.

Drug Potency Analysis

Analyze medicated feed samples for potency of drug components as specified on the collection

report.

3. Methodology

Sample Preparation for Drugs Other Than Antibiotic Drugs

- Prepare a composite by thoroughly mixing together equal portions (usually 50-100g) from each subsample. Divide the prepared composite sample into two equal portions (one is the 702(b) portion) and store under seal in air-tight containers.
- Prepare the composite sample for analysis using the procedure specific to the analyte(s) of interest, or if no specific guidance is given, refer to the general feed sample preparation guidelines described in the Association of Official Analytical Chemists (AOAC) Methods, current edition (Sections 4.1.01 and 4.1.02, Methods 965.16 and 950.02) or the International Organization for Standardization (ISO) Standards, current edition (Standards 6497-6498).
- When possible, use the AOAC methods. If the product is the subject of an approved NADA, and is found violative by a method other than one in the NADA, the medicated feed sample must be examined by methods specified in the approved NADA. Non-official methods used for regulatory analysis must be validated by including reporting method attributes.

PART V - REGULATORY/ADMINISTRATIVE FOLLOW-UP

1. Federal/State Liaison

When violative animal food that presents a threat to public (human or animal) health is encountered, go through your District's procedure to advise State feed control officials (this is typically completed through the District's State Liaison). Cooperating officials often have the interest and authority to correct violative conditions expeditiously. FDA action concerning the medicated feed mill license may also still be needed.

Arrangements should be made with States conducting animal food inspections under this program to assure that the Districts are notified promptly when violative conditions are encountered.

2. Interagency Liaison

If conditions are found that have a reasonable potential for causing violative drug residues, the Districts with an update to the OHAFO division should notify United States Department of Agriculture Food Safety and Inspection Service (USDA FSIS) to sample animals receiving the suspect medicated feed. See the Memorandum of Understanding (MOU) 225-85-8400 with USDA (FSIS and Agricultural Marketing Service (AMS)) and Environmental Protection Agency (EPA) regarding regulatory activities concerning residues of drugs, pesticides and environmental contaminants in food.

The contact information for USDA FSIS field offices can be found at the following website:

http://www.fsis.usda.gov/wps/portal/informational/districtoffices.

3. Medicated Feed Mill License Approval/Denial

Inspections of firms without any observations listed on an Form FDA 483 will be classified as No Action Indicated (NAI) and the recommendation to approve the medicated feed mill license should be forwarded to CVM's Division of Animal Feeds at MedicatedFeedsTeamMail@fda.hhs.gov.

If CGMP violations that do not have an immediate impact on public health are found, as described under this Part V.4. Voluntary Action Indicated, the inspection should be classified as VAI (non-asterisked items or asterisked items that will not immediately impact public health). This classification does not affect approval and the OHAFO division should inform CVM of their recommendation to approve the license.

Firms with CGMP deviations (21 CFR § 225.120 – 225.202) as described under this part, V.5. A, will be classified as OAI. The OHAFO division should advise both the firm and CVM that a decision is pending. The OHAFO division may recommend holding an informal meeting with the firm and CVM. A pre-meeting with CVM is recommended. The OHAFO division will not recommend approval until the CGMPs deviations have been corrected. After communication with the firm, the OHAFO division and CVM will determine if the CGMPs corrections are sufficient to warrant approval of the license and CVM will notify the firm.

In addition, violations that could impact medicated feed mill manufacturing may be a reason for the Agency to refuse issuing a medicated feed mill license. Discuss these adverse finding with the CVM.

4. Voluntary Action Indicated

When CGMP deviations (21 CFR 225) are isolated occurrences and not representative of the common practice of the firm, they may not warrant refusal to approve a license or advisory/ enforcement action. However, if reasonable voluntary compliance efforts fail to correct a continuing pattern of CGMP deviations, formal advisory or enforcement action should be considered using the Administrative/Regulatory Sanctions in Part V.5 of this compliance program.

5. Administrative/Regulatory Sanctions

The OHAFO division conducting the inspection should contact CVM as soon as egregious violative conditions are identified so that a compliance pathway can be determined prior to inspection close-out. This will aid in the accurate and efficient processing of the case. Note that all Untitled Letter and Warning Letter proposals will be reviewed by CVM. The OHAFO division should review instructions in the Regulatory Procedures Manual (RPM) regarding the clearance of Warning Letters prior to issuance.

A. Current Good Manufacturing Practice Deviations

Examples of significant CGMP violations that warrant OAI classification include:

- Failure to conduct adequate clean-out procedures which have or could result in unsafe contamination of the finished product. For example, the failure to flush or sequence after a medicated animal food manufactured with Monensin and before manufacturing a horse feed. [21 CFR § 225.65(a)]
- Scales or metering devices used to determine the amount of drug ingredient in the product are inaccurate or are operating in a manner that has caused or could be expected to cause incorrect or erratic drug levels in the medicated feed. For example, the scale used to measure all Type A medicated articles and Type B medicated feeds has not been tested for accuracy within the annual timeframe [21 CFR § 225.30(b)(4)] .
- Lack of daily drug inventory records or failure to make a daily comparison between the actual amount of drug used and the theoretical amount of drug used or failure to take corrective action when significant discrepancies are detected. For example, the firm did not perform daily reconciliation, in addition when there was a discrepancy detected, the firm did not conduct an investigation to determine the cause of the discrepancy and take corrective actions [21 CFR § 225.42(b)(7)].
- A pattern of failure to perform medicated feed assays according to the schedule in CFR § 225.58. For example, the firm manufactured a Type C Medicated Feed using a Category II Type A Medicated Article three or more times during the calendar year, and during this time, the firm assayed one or less medicated feed products for drug components during that same calendar year. [21 § CFR 225.58(b)(1)]
- Lack of follow-up action to determine and correct, where feasible, the cause of medicated feed not meeting assay specifications. For example, the firm did not conduct an investigation or take corrective action when assay results were not in accord with label specifications, or not within permissible assay limits. The out of specification assay can by on ANY medicated animal food, whether it is a Category I or II Type A medicated article, or Type B medicated feed. [21 § CFR 225.58(d) & (e)].
- Failure to properly label medicated feed. For example, lack of withdrawal instructions on labeling or operating in a manner that would favor a label mix-up. [21 CFR § 225.80]
- Failure to have master records or production records, or if such records are lacking elements that can reasonably be expected to cause an adverse effect on the finished product. For example, lack of master records that provides proper mix time for a formula which may cause the formula to be improperly mixed therefore caused the feed to be adulterated, or, lack of productions records does not allow the firm to accurately show sequencing of medicated animal foods to limit contamination. [21 CFR § 225.102]

Recommend advisory action and/or enforcement action when CGMP violations demonstrate that the methods, facilities, or controls being used by the firm cause an actual or probable adverse impact on the safety, identity, strength, quality, or purity of the finished product. In addition, action may be recommended if there are recurring deviations that indicate a pattern of non-compliance. These significant CGMP violations and recurring deviations support an OAI inspection classification. The following course of follow-up action should be considered:

1. On the initial CGMP inspection classified OAI, the OHAFO division may recommend issuing an Untitled Letter, a Warning Letter, or, in some cases, holding a regulatory meeting with the

firm (see Attachment C – Sample Warning Letter Issued by OHAFO Division to Firm). The OHAFO division has the discretion to determine whether a Warning Letter is appropriate based on the circumstances of the specific case. If a Letter is issued, it should include a statement that the letter constitutes official notice of CGMP violations as required under Section 512(m)(4)(B)(ii) of the FD&C Act. Issuance of this official notice is a prerequisite for withdrawal of the feed mill license.

2. If the CGMP re-inspection is violative and classified OAI, the OHAFO division may recommend advisory or enforcement action, e.g., regulatory meeting, Warning Letter, injunction and/or mass seizure of animal food, medicated feed and drug components.

3. If there are significant recurring violations, such as GMP deviations or the manufacture of unapproved medicated feed, and the feed mill does not implement corrective actions, the Agency may determine that the firm's feed mill license should be withdrawn. In addition to recurring GMP violations, the continued manufacturing of unapproved new animal drugs for use in a medicated feed may be considered as a reason to revoke the license. The Agency would then have to issue a notice of opportunity for a hearing (NOOH) to the most responsible individual at the firm proposing withdrawal of existing license. In this scenario, CVM will work with the OHAFO division to draft the NOOH and issue the notice to the firm.

B. Non-CGMP Violations

1. General Non-CGMP

Below are several examples of significant non-CGMP violations that may warrant an advisory or enforcement action:

- Failure to have an approved FDA medicated feed mill license when required.
- Use of unapproved drugs or unapproved combinations or levels of approved drugs.
- Illegal distribution of a Category II, Type A medicated article to any other person other than a licensed feed mill.
- Failure to adhere to the VFD requirements (see C. VFD below).
- Failure to properly label medicated feed with items such as the name and directions for use.
- Failure to register as a drug manufacturer when using drug(s) that require(s) a medicated feed mill license.

Note: Center concurrence is needed when OHAFO recommends issuance of a Warning Letter or Untitled Letter for CGMP or non-CGMP violations as outlined in Chapter 4 of the RPM (4-1-4 and 4-2-2). In addition, CVM would like to be notified of any other advisory action that OHAFO intends to take, but does not require CVM concurrence.

C. VFD

Now that additional drugs have transitioned from OTC to VFD status, some mills may not be familiar with the VFD requirements. (See Drugs with Veterinary Feed directive (VFD Marketing

Status and List of Approved New Animal Drug Applications Affected by Draft GFI #263 on the FDA CVM website.) In these situations, industry compliance with the final VFD regulation will first be obtained by education and voluntary compliance. Before recommending advisory or enforcement action the OHAFO division should contact CVM to discuss violations.

Below are examples of VFD violations and the classification they may warrant:

Voluntary Action Indicated (VAI)

- When use of the VFD drug has not been authorized by a veterinarian that has not resulted in a significant impact on public health.
- Distribution of a VFD feed without first notifying FDA of intent to distribute.
- Distribution of a VFD feed that does not conform to a lawful VFD order or does not conform to the approved labeling, but the issues are not egregious or are unlikely to have a significant impact on public health.

Official Action Indicated (OAI)

- When use of the VFD drug has not been authorized by a veterinarian resulting in a significant impact on public health.
- Manufacture of a VFD feed not in accordance with the VFD drug's approval, conditional approval, or index listing.
- Distribution of a VFD feed without first obtaining a VFD or an acknowledgment letter.
- Distribution of a VFD feed that does not conform to a lawful VFD order or does not conform to the approved labeling, and the issues are egregious and likely to have a significant impact on public health.

D. Violative Samples

If samples are in violation of the FD&C Act and applicable regulations, the OHAFO division should contact CVM to discuss if recall or enforcement action is appropriate.

E. Import

Detain imported shipments of medicated feed that appear to be in violation of the FD&C Act (see section F., below, of this part) and applicable regulations, and submit requests for CVM evaluation as a case in CMS. E-mail CVMImportRequests@fda.hhs.gov with any questions.

F. Violations of the Food Drug & Cosmetic Act

A medicated feed contains both a drug and a food, which is important to keep in mind while determining which statutory citation to charge. In many cases it may be appropriate to cite both a food and a drug charge. In other situations, it is better to focus on the charge that most closely relates to the public health impact.

1. Common Drug Adulteration Violations

a. Section 501(a)(1) If it consists in whole or in part of any filthy, putrid, or decomposed substance;

   This citation is typically used if the drug (Type A medicated article) is actually adulterated with some substance or filth.

b. Section 501(a)(2)(A) if it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health;

   This citation is typically used when there has been a failure in CGMPs or other practices that may result in the drug (Type A medicated article) becoming contaminated or adulterated.

c. Section 501(a)(5) if it is a new animal drug which is unsafe within the meaning of section 360b of this title;

   This citation is typically used if the new animal drug is deemed unsafe because it is not approved, conditionally approved, or indexed, or it is not used in conformance with the approval, conditional approval, or index listing. If you are using this citation, you also need to cite the reason the new animal drug is considered unsafe under section 512 of the FD&C Act. An example may be the use of a VFD drug not in conformance with the VFD requirements. If the new animal drug has already been used in or on animal feed, the preference is to use the citation in 501(a)(6), which is more specific to that situation.

d. Section 501(a)(6) if it is an animal feed bearing or containing a new animal drug, and such animal feed is unsafe within the meaning of section 360b of this title.

   This citation is typically used when an animal feed contains a new animal drug that is deemed unsafe because it is not approved, conditionally approved, or indexed, or it is not used in conformance with the approval, conditional approval, or index listing. If you are using this citation, you also need to cite the reason the animal food containing the new animal drug is considered unsafe under section 512 of the FD&C Act. Examples may include: (1) use of new animal drugs that are not approved for use in medicated feed; (2) use of new animal drugs in medicated feed for species not approved (see CPG 615.115 for additional consideration); (3) use of new animal drugs in the medicated feed in combinations that are not approved; (4) use of new animal drugs in the medicated feed at levels that are not approved (5) use of a VFD feed not in conformance with the VFD requirements.

2. Common Drug Misbranding Violations

a. Section 502(a) False or misleading label. If labeling is false or misleading in any particular…

   If there is another misbranding citation that is applicable (e.g., the requirement that the label bears the established name, or failure to include necessary caution statements) then we prefer to use the more specific citation.

b. Section 502(e)(1)(A)(i) if it is a drug, unless its label bears … the established name (as defined in subparagraph (3)) of the drug, if there is such a name …

   This citation is typically used when a medicated feed does not include the established name of the drug.

c. Section 502(e)(1)(A)(ii) if it is a drug, unless its label bears … the established name and quantity or, if determined to be appropriate by the Secretary, the proportion of each active ingredient…

   This citation is typically used when a medicated feed does not include the amount of the active drug ingredient in the medicated feed, or if it indicates an incorrect amount.

d. Section 502(f)(1) unless its labeling bears adequate directions for use…

   This citation is typically used when the label does not contain information that would allow it to be used appropriately. Examples include: (1) adequate feeding directions; (2) caution statements required by the approval; and (3) information required by the VFD requirements.

3. Food adulteration violations

Generally use the food adulteration violations when an animal food is adulterated for a reason that does not have to do with it being medicated feed or improper use of a new animal drug. For example, if the animal food is adulterated because of an unsafe food additive.

a. Section 402(a)(1) If it bears or contains any poisonous or deleterious substance which may render it injurious to health.

   This citation is typically used when there is evidence the animal food contains a harmful substance. Note that there is a different burden when the harmful substance is naturally occurring versus when it is something that is added to the animal food.

b. Section 402(a)(2)(C)(i) if it is or if it bears or contains any food additive that is unsafe within the meaning of section 348 of this title…

   This citation is typically used when an unapproved food additive has been added to the animal food or when an approved food additive is not being used in conformance with the food additive approval.

c. Section 402(a)(2)(C)(ii) if it is or if it bears or contains … a new animal drug (or conversion product thereof) that is unsafe within the meaning of section 360b of this title…

   This citation is typically used when a non-medicated feed is contaminated by a medicated article or medicated feed (e.g., improper drug carryover into a non-medicated feed).

d. Section 402(a)(3) if it consists in whole or in part of any filthy, putrid, or decomposed substance, or if it is otherwise unfit for food…

This citation is typically used in animal food in situations where an animal food or animal food ingredient is not appropriate to be used as animal food.

e. Section 402(a)(4) if it has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health;

This citation is typically used when an animal food may become adulterated because of insanitary practices at the facility. This citation will be used when a facility has failed to comply with the new Preventive Controls for Animal Food CGMPs and/or hazard analysis and risk-based preventive control requirements after the relevant compliance date (21 CFR part 507).

f. Section 301(mm) for failure to file a reportable food registry

This citation is typically used when a facility fails to file a reportable food registry as required for a reportable animal food.

4. Food misbranding violations.

a. Section 403(a)(1) If its labeling is false or misleading in any particular…

If there is another misbranding citation that is applicable (e.g., the requirement that the label bears the established name, failure to include necessary caution statements) then we prefer to use the more specific citation.

b. Section 403(e) If in package form unless it bears a label containing (1) the name and place of business of the manufacturer, packer, or distributor; and (2) an accurate statement of the quantity of the contents in terms of weight, measure, or numerical count ….

This citation is typically used when a packaged animal food does not have a label, or the label does not include the manufacturer, packer, or distributor information or does not include the quantity or weight.

c. Section 403(i) Unless its label bears (1) the common or usual name of the food, if any there be, and (2) in case it is fabricated from two or more ingredients, the common or usual name of each such ingredient …

This citation is typically used when an animal food label does not include the common or usual name of the food or its ingredients.

PART VI - REFERENCES, ATTACHMENTS AND PROGRAM

CONTACTS

1. Applicable References or Aids

1. 21 CFR part 11, Electronic Records; Electronic Signatures
2. 21 CFR part 207, Requirements for Foreign and Domestic Establishment Registration and Listing for Human Drugs, Including Drugs that are Regulated Under a Biologics License Application, and Animal Drugs, and the National Drug Code
3. 21 CFR part 225, Current Good Manufacturing Practice for Medicated Feeds
4. 21 CFR part 507, Current Good Manufacturing Practices, Hazard Analysis, and Risk-Based Preventative Controls for Food for Animals
5. 21 CFR part 515, Medicated Feed Mill License
6. 21 CFR part 558, New Animal Drugs for Use in Animal Feeds
7. 21 CFR part 558.4, Requirement of a medicated feed mill license
8. 21 CFR part 558.6, Veterinary feed directive drugs
9. Animal Drug Availability Act of 1996
10. BSE Compliance Program, CP 7371.009
11. CPG 160.100, Regulatory Actions and Small Business
12. CPG 615.200, Proper Drug Use and Residue Avoidance by Non-Veterinarians
13. CPG 615.115, Extra-Label Use of Medicated Feeds for Minor Species
14. CPG 625.500, Failure to Register (Withdrawn 2/20/2020)
15. CPG 666.100, Alternate Feeding of Different Medicated Feeds
16. CPG 680.200, CGMP Regulations for Medicated Feeds - Daily Inventory Requirements
17. CPG 680.500, Unsafe Contamination of Animal Feed from Drug Carryover
18. CPG 680.600, Sequencing as a Means to Prevent Unsafe Drug Contaminants in the Production, Storage, and Distribution of Feeds
19. CPG 689.100, Direct-Fed Microbial Products
20. FDA/CVM Guidance for Industry #72: GMP's For Medicated Feed Manufacturers Not Required to Register and Be Licensed with FDA
21. FDA/CVM Guidance for Industry #120, Small Entity Compliance Guide, Veterinary Feed Directive Regulation Questions and Answers
22. FDA/CVM Guidance for Industry #213, New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicted Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209
23. FDA/CVM Guidance for Industry #235: Current Good Manufacturing Practice Requirements for Food Animals
24. FDA/CVM Guidance for Industry #263: Recommendations for Sponsors of Medically Important Antimicrobial Drugs Approved for Use in Animals to Voluntarily Bring Under Veterinary Oversight All Products That Continue to be Available Over-the-Counter
25. Feed Additive Compendium, The Miller Publishing Co., Minneapolis, MN, current edition.
26. Feed Contaminants Program, CP 7371.003
27. Field Bulletin #60: Biosecurity procedures feed facilities
28. Import Detention Violation Codes
29. Investigations Operations Manual
30. List of Approved New Animal Drug Applications Affected by Draft GFI #263

31. MOU with USDA and EPA *MOU 225-85-8400 - MOU with USDA (FSIS and AMS) and EPA regarding regulatory activities concerning residues of drugs, pesticides and environmental contaminants in foods*
32. Official Methods of Analysis of the Association of Official Analytical Chemists, current edition
33. Official Publication (current edition), Association of American Feed Control Officials, Inc.
34. Regulatory Procedures Manual
35. Type A Medicated Article Compliance Program, CP 7371.005
36. VFD Inspection Tool (available with current field assignment)

2. Attachments

1. Attachment A: Sample Form Letter Issued by the OHAFO Division to Firm to Request Voluntary Withdrawal of Approved Medicated Feed Mill License
2. Attachment B: Form Letter for Firms to Voluntarily Withdraw Approved Medicated Feed Mill License
3. Attachment C: Sample Warning Letter Issued by OHAFO Division to Firm

3. Program Contacts

a. ORA Contacts

Inspectional inquiries:

- FDA personnel should direct inspection inquiries to:
  Office of Human and Animal Food Operations (OHAFO)/OHAFOW/DDHAFO/DHAFOBDHAFOB
  E-mail: lourdes.andujar@fda.hhs.gov
  Phone: 787-729-9010; 787-238-0114 (BB)

- State personnel should direct inspectional inquiries to:
  State Liaisons at their District Office

Import Operations inquiries:

- FDA personnel should direct import operations inquiries to:
  Office of Enforcement and Import Operations/Division of Import Operations Management (ORA/OEIO/DIOM)
  E-mail: Percal.Lopez@fda.hhs.gov
  Phone: 956-630-0917 x1003

Direct questions about laboratory methodology to:

- ORA/ORS/Office of Food and Feed Laboratory Operations/Food & Feed Scientific Staff (OFFLO/FFSS)
  E-mail: Srinivasulu.Chigurupati@fda.hhs.gov
  Phone: 240-402-4815

Direct resource inquiries to:

- Office of Operations/Office of Management
  Phone: 240-402-8102

b. Center Contacts

- Program and Administrative Inquiries
  Division of Compliance
  E-mail: CVMAnimalFoodPrograms@fda.hhs.gov
  Phone: 240-402-7001

- GMP and Labeling Inquiries
  Division of Animal Feeds
  Medicated Feed Specialist
  E-mail: CVMAnimalFoodPrograms@fda.hhs.gov
  Phone: 240-402-7077

- Program Manager
  Division of Compliance
  E-mail: CVMAnimalFoodPrograms@fda.hhs.gov
  Phone: 240-402-7001

- Compliance Inquiries
  Division of Compliance
  E-mail: CVMAnimalFoodPrograms@fda.hhs.gov
  Phone: 240-402-7001

Attachment A - Sample Form Letter Issued by OHAFO Division to Firm to Request Voluntary Withdrawal of an Approved Medicated Feed Mill License

OHAFO Division Letterhead

RESPONSIBLE INDIVIDUAL, TITLE
FIRM NAME
FIRM MAILING ADDRESS

Dear_____:

You are subject to the requirements of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and the regulations under which they are promulgated. If you hold a medicated feed mill license, Form FDA 3448, the FD&C Act and regulations require you to register as a drug establishment with the Food and Drug Administration (FDA) and make you subject to periodic inspections by FDA to verify your compliance with the Current Good Manufacturing Practice for Medicated Feeds as published in Title 21 of the Code of Federal Regulations part 225 (21 CFR 225).

However, if you no longer manufacture medicated feed requiring a medicated feed mill license and do not plan to do so in the future, you may cancel your drug establishment registration and request the withdrawal of the license without prejudice. With the withdrawal of the license, you would be exempt from drug establishment registration with the FDA.

Please be aware that if your license is withdrawn, you may not legally mix medicated feed that are required to be manufactured in a licensed feed mill. Should you subsequently wish to manufacture or mix a medicated feed that is required to be manufactured in a licensed feed mill, you will be required to register the mill and submit a Medicated Feed Mill License Application.

This inquiry is to aid the FDA in maintaining an inventory of only those firms actively engaged in mixing medicated feed that require a license.

If these circumstances fit your situation, complete and return the enclosed letter to the Center for Veterinary Medicine requesting the withdrawal of your medicated feed mill license.

Sincerely yours,

District Director/ OHAFO Program Division Director

cc: HFV-220

Attachment B – Form Letter for Use by Firm to Voluntarily Withdraw Approved Medicated Feed Mill License

FDA/CVM
Division of Animal Feeds, HFV-220
12225 Wilkins Avenue
Rockville, MD 20852
E-mail: MedicatedFeedsTeamMail@fda.hhs.gov

Sir or Madam:

By authority of this letter, please do the following on my behalf:

___withdraw the approved medicated feed mill license (Form FDA 3448)
Medicated feeds that are required to be manufactured by a licensed medicated feed mill are no longer mixed by me. I understand that I must re-register with FDA and re-apply for a medicated feed mill license if I should subsequently wish to manufacture or mix medicated feed that are required to be manufactured by a licensed medicated feed mill. I will comply with the requirements to electronically withdraw the drug establishment registration.

Drug Establishment Registration Number (FEI) _____

DUNS Number _____

Medicated Feed Mill License Number _____

Manufacturing Site Legal Business Name _____

Address _____

City, State Zip _____

Sincerely,
Signature _____

Printed name _____

Title _____ Date _____

Attachment C - Sample Warning Letter Issued by OHAFO Division to Firm

OHAFO Division Letterhead

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

RESPONSIBLE INDIVIDUAL, TITLE
FIRM NAME
FIRM MAILING ADDRESS

Dear_____:

An inspection of your medicated feed mill located at_____was conducted by a Food and Drug Administration investigator on _____. [Describe reason for inspection/scope of inspection].

Instructions: The body of the letter should discuss the violations of the FD&C Act in the order of impact to public health. This template includes template language denoted by brackets [], for medicated feed CGMP violations as well as other statutory violations commonly observed at medicated feed mills, replace bracketed template language with facts and evidence from the case file. Remove or add violation paragraphs as applicable to the situation. See V.5 for descriptions of additional common violations and use a similar format structure to develop additional violation paragraphs that may be applicable.

[You have manufactured a medicated feed that is [subpotent/superpotent] in violation of the FD&C Act. On [Date], you manufactured [formulation name] containing the new animal drug(s) [drug name]. [Insert any additional relevant facts from the inspection that demonstrate why the formulation was subpotent/superpotent.] [Drug name] is approved for use in medicated feed for [species/class] at a level of [drug level]. [Describe the public health impact (superpotent – potential for overmedication of animal and tissue residue, subpotent – animal's health may suffer from not getting the correct dosage] As a result, your medicated feed is unsafe under section 512(a)(2)(A) of the Act (21 U.S.C. § 360B(a)(2)(A)), and adulterated under section 501(a)(6) of the Act (21 U.S.C. § 351(a)(6)), because [formulation name] containing [drug name] was [subpotent/superpotent]. [Describe any corrective actions taken and address the adequacy of the response.]]

[You have [manufactured/labeled] a medicated feed in a way that did not conform with the drug's approval, which is a violation of the FD&C Act. On [Date], you manufactured

[formulation name] containing the new animal drug(s) [drug name(s)]. [Insert any additional relevant facts from the inspection that demonstrate why the formulation/labeling did not conform to the approval]. [Describe the relevant approval information (Drug X is approved for use in Y species at Z rate. Drug A is approved for use in B species at C rate.] [Describe why the use doesn't conform (There is no approval for the use of these drugs in combination in a medicated feed. The drug is not approved for use for this indication/species).]. As a result, your medicated feed is unsafe under section 512(a)(2)(A) of the Act (21 U.S.C. § 360B(a)(2)(A)), and adulterated under section 501(a)(6) of the Act (21 U.S.C. § 351(a)(6)) because [formulation name] containing [drug name] was not [manufactured/labeled] in conformance with [drug name's] approval.] [Describe any corrective actions taken and address the adequacy of the response.]]

[This inspection documented significant deviations from the Current Good Manufacturing Practice (CGMP) regulations for [licensed medicated feed manufacturers, Title 21, Code of Federal Regulations, Part 225 (21 CFR 225.10 - 225.115)/non-licensed medicated feed manufacturers, Title 21, Code of Federal Regulations, Part 225 (21 CFR 225.120-202]. As a result of these deviations, the medicated feed manufactured, processed, packed, or held at your facility is adulterated under section 501(a)(2)(B) of the FD&C Act (21 U.S.C. § 351(a)(2)(B)). Violations observed during the inspection include, but are not limited to, the following:

Instructions: If there are multiple violations use a numbered list to discuss each CGMP violation. State what the violation is and end with the CFR citation. Describe the observation(s) and evidence that demonstrate the violation occurred. A bulleted list may help organize multiple observations for the same violation. Describe any corrective actions taken and address the adequacy of any on-site response or written response. See examples below.

1. Your firm failed to maintain the drug inventory by means of a daily comparison of the actual amount of drug used with the theoretical drug usage. In addition, you failed to investigate and take corrective action on significant discrepancies, and to detain affected medicated feeds remaining on the premises until the discrepancy was reconciled, as required by 21 CFR 225.42(b)(7). Specifically:

    Our inspection found, your daily drug inventory records provide no documentation of reconciliation of actual versus theoretical weights were performed. Furthermore, significant discrepancies in daily drug inventories were not investigated and corrective actions were not implemented. For example on February 22, 2016, the new animal drug Monensin (Rumensin 90) drug inventory documented 53 pounds on hand. A review of this record by FDA, which included manual calculation on the values entered on this record, indicate that you had on hand 43 pounds of this drug. In addition, on February 3, 2016, your drug inventory record for the new animal drug Lasalocid (Bovatec 91) shows two significant discrepancies. There is no record of investigation or corrective action performed on these discrepancies.

We acknowledge that in your response to the form FDA 483 you indicated you have revised your "*drug addition"* SOP to adjust for the tare weight of the empty bag prior to weighing a new bag, revised your batch sheets to increase your staff awareness to recorded drug use, possible variances and identified corrective actions, and trained your staff in this new policy. We will evaluate the adequacy of these corrective actions upon our next inspection of your facility.

2. Your firm did not perform the required assays of medicated feeds. For feeds that require a medicated feed mill license, representative samples of medicated feed containing each drug, or drug combination shall be collected and assayed by approved official methods, at periodic intervals during the calendar year. At least one of these assays shall be performed on the first batch using the drug. 21 CFR 225.58(b)(1). For example:

    - The first batch of [formulation name] containing [drug name] was manufactured on [date]. Your firm did not perform a drug assay on the first batch of feed containing this drug or any subsequent batches manufactured during calendar year [year].
    - The first batch of [formulation name] containing [drug name] was manufactured on [date]. Your firm failed to perform a drug assay on the first batch of feed containing this drug or any subsequent batch manufactured up to the start of this inspection.

Your [date] response to the 483 did not include any corrective actions for these violations.]

[Your firm is not currently registered with the Agency as a drug establishment as required under section 510(j) of the Act, 21 U.S.C. § 360(j). Therefore, all medicated feeds manufactured at your facility are misbranded under section 502(o) of the Act, 21 U.S.C. § 352(o). [Describe any corrective actions taken and address the adequacy of the response.]]

[Your firm failed to submit a report to the Reportable Food Registry (RFR) for [formulation name]. [Describe evidence that supports why the food was reportable and how they failed to meet the reportable food requirements (e.g., didn't file, filed after 24 hours)] A responsible party (the person who is required to file a food facility registration) is required to file a report when there is a reasonable probability that the use of, or exposure to, an article of food will cause serious adverse health consequences or death to humans or animals. Such foods are "Reportable Foods." Failure to submit a required report about a reportable food is a prohibited act under section 301(mm) of the Act (21 U.S.C. § 331(mm)). [Describe any corrective actions taken and address the adequacy of the response.]]

The above is not intended as an all-inclusive list of violations. As a manufacturer of medicated and non-medicated feeds, you are responsible for assuring that your overall

operation and the products you manufacture and distribute are in compliance with the law.

You should take prompt action to correct these violations, and you should establish procedures to prevent the recurrence of these violations. Failure to promptly correct these violations may result in regulatory and/or administrative sanctions. These sanctions include, but are not limited to, seizure, or injunction. [*For licensed medicated feed mills include the following to the list of sanctions* [and/or notice of opportunity for a hearing on a proposal to withdraw approval of your medicated feed mill license under section 512(m)(4)(B)(ii) of the FD&C Act and 21 CFR 515.22(c)(2)]].

[*Include if mill is licensed and there were CGMP violations:* Based on the results of the (date) inspection, evaluated together with the evidence before FDA when the medicated feed mill license was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of medicated feeds are inadequate to assure and preserve the identity, strength, quality, and purity of the new animal drugs therein. This letter constitutes official notice under the law and provides you an opportunity to correct the above deficiencies.]

[*Include if re-inspection fees are warranted:* Section 743 of the Act (21 U.S.C. 379j-31) authorizes FDA to assess and collect fees to cover FDA's costs for certain activities, including reinspection-related costs. A reinspection is one or more inspections conducted subsequent to an inspection that identified noncompliance materially related to a food safety requirement of the Act, specifically to determine whether compliance has been achieved. Reinspection-related costs means all expenses, including administrative expenses incurred in connection with FDA's arranging, conducting, and evaluating the results of the reinspection and assessing and collecting the reinspection fees (21 U.S.C. 379j-31 (a)(2)(B)). For a domestic facility, FDA will assess and collect fees for re-inspection-related costs from the responsible party for the domestic facility. The inspection noted in this letter identified noncompliance materially related to a food safety requirement of the Act. Accordingly, FDA may assess fees to cover any re-inspection-related costs.]

You should notify this office, in writing, within fifteen (15) working days of the receipt of this letter of the steps you have taken to bring your firm into compliance with the law. Your response should include an explanation of each step being taken to correct the violations and prevent their recurrence. If corrective action cannot be completed within 15 working days, state the reason for the delay and the date by which the corrections will be completed. Include copies of any available documentation demonstrating that corrections have been made.

Your response should be directed to _____ at the above address.

Sincerely yours,

District Director/ OHAFO Program Division Director

bcc:
ADDITIONAL RESPONSIBLE INDIVIDUALS
HFV-220
HFV-230

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